# Many Told to Stop Treatment

**Asthma** *from page 1*

tients about their asthma symptoms, make sure they're taking their medications, and have them use their peak flow meters, he said in an interview.

It is safer for pregnant women with asthma to be treated with asthma medications than it is for them to have asthma symptoms and exacerbations, according to the guidelines.

"It's surprising how many physicians, including obstetricians and family practitioners, will tell their patients that when they're pregnant, they should stop all their medications," Dr. Dombrowski said, explaining that inappropriate reduction of therapy could cause the woman to become hypoxic and injure her fetus.

**Tailor medications to asthma severity. Give mild asthma patients low-dose inhaled corticosteroids. For more severe disease, ramp up the corticosteroids.**

The step-care therapeutic approach increases the number and dosage of medications with increasing asthma severity. (See box.) At each step of therapy, medications are considered preferred or alternative, based on efficacy and safety considerations, according to the authors.

"Patients whose symptoms are not optimally responding to treatment should receive a step up in treatment to more intensive medical therapy. Once control is achieved and sustained for several months, a step-down approach can be considered, but a change in therapy should be undertaken cautiously and administered gradually to avoid compromising the stability of the asthma control," they wrote.

Among other recommendations of the ACOG panel:

► Budesonide is the preferred inhaled corticosteroid for use during pregnancy.

► Inhaled albuterol is recommended rescue therapy for pregnant women with asthma.

► Continuation of immunotherapy is recommended in patients who are at or near a maintenance dose, not experiencing adverse reactions to the injections, and apparently deriving clinical benefit.

► Use of prednisone, theophylline, antihistamines, inhaled corticosteroids, $\beta_2$-agonists, and cromolyn is not contraindicated for breastfeeding.

► Identifying and controlling or avoiding factors such as allergens and irritants, particularly tobacco smoke, can lead to improved maternal well-being with less need for medication.

"By reducing trigger exposures you can reduce symptoms," said Dr. Dombrowski, who is also a professor at Wayne State University, Detroit. He described a patient who had 100 stuffed animals in her college dormitory room. "After I had her get rid of the stuffed animals and put covers on her mattress and pillows, her asthma disappeared and we were able to stop all medications."

On the basis of consensus and expert opinion, the ACOG panel also concluded that asthma control is enhanced by self-management skills, including self-monitoring, correct use of inhalers, and following a plan for long-term management.

"For pulmonary function assessment of patients during outpatient visits, spirometry is preferable, but peak expiratory flow measurement with a peak flow meter also is sufficient," they said.

Dr. Dombrowski's take-home message to physicians is this: Tailor medications to asthma severity. That means giving a woman with mild asthma a course of low-dose inhaled corticosteroids. For more severe disease, the inhaled corticosteroids can be ramped up and supplemented with other medications to control the asthma.

"One size does not fit all, and by tailoring medications we can decrease risk to the fetus," he said, adding that if treating physicians are worried about fetal medication exposure, they can reduce it appropriately.

The new asthma management guidelines are the first to be promulgated by ACOG, said Dr. Dombrowski.

In creating the management guidelines, the ACOG panel drew on eight uncontrolled prospective studies, as well as data from multiple time series and the opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. ■

## Step Therapy Advised During Gestation

**Mild Intermittent Asthma**
No daily medications, albuterol as needed.

**Mild Persistent Asthma**
Preferred—Low-dose inhaled corticosteroid.
Alternative—Cromolyn, leukotriene receptor antagonist, or theophylline (serum level 5-12 mcg/mL).

**Moderate Persistent Asthma**
Preferred—Low-dose inhaled corticosteroid and salmeterol or medium-dose inhaled corticosteroid or (if needed) medium-dose inhaled corticosteroid and salmeterol.
Alternative—Low-dose or (if needed) medium-dose inhaled corticosteroid and either leukotriene receptor antagonist or theophylline (serum level 5-12 mcg/mL).

**Severe Persistent Asthma**
Preferred—High-dose inhaled corticosteroid and salmeterol and (if needed) oral corticosteroid.
Alternative—High-dose inhaled corticosteroid and theophylline (serum level 5-12 mcg/mL) and oral corticosteroid if needed.

Source: ACOG Practice Bulletin Number 90; Obstet. Gynecol. 2008;11:457-9

## Drugs, Pregnancy, and Lactation

# Exposure to Monoclonal Antibodies

Excluding those classified as orphan drugs, there are 10 monoclonal antibodies currently used to treat cancer, asthma, or rheumatoid arthritis. Five are composed of various types of humanized immunoglobulin G (IgG) and two of murine IgG. The approved indications include leukemia, metastatic carcinoma of the colon or rectum, squamous cell carcinoma of the head and neck, non-Hodgkin's lymphoma, metastatic breast cancer, and moderate to severe chronic diseases such as asthma and rheumatoid arthritis.

The antineoplastic agents are alemtuzumab (Campath), bevacizumab (Avastin), cetuximab (Erbitux), gemtuzumab ozogamicin (Mylotarg), ibritumomab tiuxetan (Zevalin), panitumumab (Vectibix), tositumomab and iodine 131 (Bexxar), and trastuzumab (Herceptin). The ninth member of this group, rituximab (Rituxan), is also used as an antirheumatic agent.

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Exposure of the embryo and fetus should be expected whenever these antibodies are used in pregnancy. Although their molecular weights are very high, two are known to cross the placenta: Rituxan in humans and Herceptin in monkeys. The transplacental passage of the other antibodies has not been studied, but endogenous IgG crosses the placenta. Moreover, the long elimination half-lives ranging from about 2 to 19 days will place these antibodies at the maternal-fetal interface for prolonged periods. Animal reproduction studies have not been conducted with Bexxar, Campath, Erbitux, or Zevalin. Studies in pregnant animals with Herceptin and Rituxan suggested low risk for humans, whereas the suggested risk was higher for Avastin, Mylotarg, and Vectibix.

Bexxar, Campath, Erbitux, Mylotarg, Zevalin, and Rituxan may cause severe, infusion-related toxicity, including hypotension. Although premedication is used to lessen this effect, this toxicity could have deleterious effects on placental perfusion, resulting in harm to the embryo and fetus.

Human pregnancy data are available only for Herceptin and Rituxan. For Herceptin, the human pregnancy experience is limited to five cases, two of which involved first-trimester exposure. Although no congenital malformations were observed, fetal renal toxicity, as evidenced by oligohydramnios or anhydramnios, was observed in three cases. The toxicity might have been caused by inhibition of human epidermal growth factor receptor 2 (HER-2) in the fetal kidneys. The renal toxicity was reversible, and all five infants developed normally. However, there is potential for other toxicity because HER-2 protein expression is high in many embryonic tissues, such as cardiac and neural tissues.

Six pregnancies have been exposed to Rituxan, including two in the first trimester. No structural anomalies were noted, and all infants appeared to be healthy at birth. One had depletion of B lymphocytes, but B-cell counts returned to normal at about 4 months of age. No increase in infectious disease was noted in any of the infants.

Reports of exposure to Bexxar and Mylotarg during pregnancy are unlikely. Bexxar, indicated for non-Hodgkin's lymphoma, contains radioactive iodine and is contraindicated in pregnancy. Mylotarg, a combination of gemtuzumab (IgG4k) conjugated with the cytotoxic antitumor antibiotic calicheamicin, is indicated for the treatment of patients with CD33-positive acute myeloid leukemia in first relapse who are 60 years of age or older. Mylotarg caused significant developmental toxicity at a small fraction of the human dose in the only experimental animal species tested. The therapeutic regimen for Zevalin, another agent for non-Hodgkin's lymphoma, should preclude its use in pregnancy because it includes two radioactive components as well as Rituxan, and the risk to the embryo and fetus appears to be high.

Omalizumab (Xolair), a monoclonal antibody used for moderate to severe persistent asthma, selectively binds to human IgE and has a half-life of 26 days. It has not been studied in animals or humans, but probably crosses the placenta. Reproduction studies in monkeys suggest that the risk in human pregnancy is low, but the human pregnancy experience is limited. In clinical trials, 29 women became pregnant during treatment with Xolair, which was stopped when pregnancy was diagnosed. Among these patients, there were 4 spontaneous abortions (SABs), 3 elective abortions, 11 normal deliveries, and 11 ongoing pregnancies. The number of SABs, all occurring in the first trimester, is within the expected incidence for recognized pregnancies.

A full assessment of the risk of monoclonal antibodies during pregnancy is not possible because of the very limited or absent human pregnancy data, including a lack of long-term evaluation of exposed offspring. Nevertheless, these agents are used for life-threatening diseases and, if indicated, should not be withheld from a pregnant woman—with the exception of Bexxar, Mylotarg, and possibly Zevalin. ■

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